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TITLE: **CD34** splice variant: an attractive marker for selection of gene-modified cells.
AUTHOR: Fehse B; Richters A; Putimtseva-Scharf K; Klump H; Li Z; Ostertag W; **Zander A R**; Baum C
CORPORATE SOURCE: Bone Marrow Transplantation, Heinrich-Pette-Institute for Experimental Virology and Immunology, Martinistrasse 52, Hamburg, D-20246, Germany.
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AB This study presents a promising selection system for gene-modified cells other than human hematopoietic progenitor and endothelial cells based on transgenic expression of human **CD34**. Three retrovirally transduced variants of **CD34** were compared, differing in the length of their cytoplasmic domains. These were the full-length transmembrane protein (flCD34), a truncated form (tCD34) that is found as a naturally occurring splice variant and has a partial deletion of the cytoplasmic domain for signal transduction, and an engineered variant which is completely deprived of its cytoplasmic tail (dCD34). All three variants allowed selection of gene-modified cells using commercially available immunoaffinity technology. However, examination by flow cytometry as well as by Southern, Northern, and Western blot revealed that dCD34, as opposed to tCD34, is not stably anchored in the membrane and thus is expressed at low levels on the surface of transduced cells. Therefore, tCD34 was chosen as the more promising candidate for a clinically applicable **cell surface marker**.
We show that gene-modified human primary T lymphocytes expressing tCD34 can be enriched to high purity (>95%) using clinically approved immunoaffinity columns. In addition, we demonstrate the utility of tCD34 for surface marking of murine hematopoietic cells in vivo, including primary T lymphocytes detected 9 weeks after bone marrow transplantation.

L4 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
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TITLE: In vivo studies on the effect of expressing naturally occurring truncated **CD34** on hematopoietic progenitors and differentiated blood cells.
AUTHOR(S): Fehse, B. [Reprint author]; Schiedlmeier, B.; Li, Z.; Klump, H.; Wahlers, A.; Putimtseva-Scharf, K. [Reprint author]; Ostertag, W.; **Zander, A. R.** [Reprint author]; Baum, C.
CORPORATE SOURCE: Bone Marrow Transplantation, University Hospital Eppendorf, Hamburg, Germany
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AB We recently demonstrated the usefulness of a naturally occurring splice variant of human **CD34** with a shortened intracellular domain (tCD34) as a **gene transfer marker.** Expression of tCD34 allows marking of gene-modified cells that normally do not express **CD34,** and their tracking by flow cytometry. In addition, gene-modified cells could be enriched to high purity using magnetic cell sorting (MACS) devices approved for clinical use (Molecular Therapy 1, 448-456). Truncated **CD34** lacks most of the putative signal transduction domains of **CD34;** however, a possible interference with cellular functions especially in hematopoietic cells could not be excluded per se. We therefore analyzed the impact of tCD34 expression on hematopoietic stem cell engraftment and differentiation in a mouse model (C57Bl/6). Control mice received marrow transduced with retroviral vectors expressing the full-length protein of human **CD34,** human truncated nerve growth factor receptor, or enhanced green fluorescent protein. We found that in mice transplanted with retrovirally transduced bone marrow cells tCD34 was detectable by flow cytometry in all hematopoietic lineages at constant levels (up to 50%) during the whole period of observation (7 months), similar to the efficiency obtained with the other markers tested. In vitro activation of peripheral blood lymphocytes which were mostly tCD34-negative led to a strong increase in transgene-expressing cells. For serial transplantation, bone marrow cells were enriched by MACS to high purity (>90%) based on the expression of human tCD34. A first analysis of those mice after 10 weeks demonstrated that all lineages of hematopoiesis were normally reconstituted and almost exclusively tCD34-positive. We are currently investigating the influence of tCD34 expression on behavior and differentiation potential of human **CD34**+ progenitor cells. In summary, the present study may generate new insights regarding the functional role of tCD34 in hematopoiesis and its potential utility as a **cell surface marker** for human gene therapy.